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EDITORIAL REVIEWS

Pseudo 2:1 Atrioventricular Block and T Wave Alternans in the Long QT Syndromes

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The extreme prolongation of ventricular action potential duration that occurs in some of the long QT syndromes may result in two forms of alternating activity of the heart: a "pseudo" 2:1 atrioventricular (AV) block and a T wave alternation, both of which are rate dependent. The pseudo 2:1 AV block relates to the extreme prolongation of ventricular refractoriness. The T wave alternation reflects the fact that the rate dependence of action potential duration differs in degree or magnitude in the subendocardial and subepicardial layers of the ventricular wall. Examples of two cases previously reported in the Journal by Weintraub et al. are used to illustrate and discuss these manifestations.

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In the September 1990 issue of the Journal, the report by Weintraub et al. (1) on 23 children with a congenital long QT syndrome includes two particularly intriguing observations that invite further discussion.

Pseudo 2:1 Atrioventricular (AV) Block

In their Figure 1 (see our Fig. 1), the authors (1) describe an "electrocardiogram at 4 days of age showing extreme QT prolongation (QT interval 840 ms) associated with *2:1 atrioventricular block*." However, given that the sinoatrial cycle length (500 to 600 ms) is much shorter than the QT interval, every other P wave must necessarily fall during or before the preceding T wave, as is clearly apparent for P_1 and P_3 (as well as all the other "even" P waves in the complete tracing). When such impulses reach the ventricle, the ventricular muscle must be absolutely refractory. Therefore, this 2:1 response is caused not by a true block of conduction but rather by simple interference (2). It is thus probably more correct to refer to the case in Figure 1 as an example of *pseudo 2:1 AV block* (3–6) because there is no evidence of any intrinsic abnormality of AV conduction. Six other reported cases of 2:1 AV block (three in Ref 7 and one each in Ref 8 to 10) can also be shown to be typical examples of pseudo 2:1 AV block. In all of them, as in the case in Figure 1, the PP intervals are much shorter than an extremely prolonged QT interval. This kind of response appears to be unique to the congenital long QT syndrome in which, in contrast to the normal situation, refractoriness may last much longer in the ventricle than in the AV transmission system.

Other abnormalities of AV conduction. Scattered cases have been reported (11–15) in which the long QT syndrome was apparently associated with other abnormalities of AV conduction. An example of true 2:1 AV block was reported (11) but as a transient event following an episode of ventricular fibrillation. Isolated examples of long QT syndrome with coexisting congenital complete heart block have been described (12,13), but the association may be merely coincidental because not a single example of this combination was found in a recent review (16) of 196 patients with the idiopathic long QT syndrome. The case reported by Weber et al. (15) was a single example of AV dissociation due to a junctional rhythm in the presence of sinus bradycardia. With the exception of this technically disputable study (15), available information indicates that the AV transmission system is little or not at all involved in the congenital long QT syndrome. Because intraventricular block, either organic or functional, also seems to be a rarity (16,17), these data suggest that the entire His-Purkinje system fails to share in the prolongation of the action potential duration (17–20) that characteristically occurs at the ventricular level. This difference may have strong pathogenic connotations because why should anything (whatever it is) that prolongs the action potential duration in ventricular muscle spare the Purkinje tissue? A successful explanation of the congenital long QT syndrome cannot escape this question.

T Wave Alternans

Duration of action potentials in subendocardium versus subepicardium. Alternation of the T wave has been considered "surprisingly" common (21) and even "characteristic" (22) of the idiopathic QT syndrome. It has been diversely attributed to a "metabolic abnormality" (23), "an abrupt increase in sympathetic discharge" (22), afterdepolariza-

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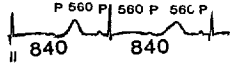
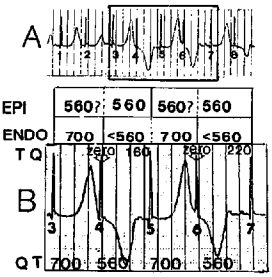


Figure 1. Pseudo 2:1 atrioventricular block (reproduced with modification from Fig. 1, Ref. 1). The QT interval (840 ms) is much longer than the sinoatrial cycle length (560 ms). P_1 and P_2 (every other P wave in the full tracing) occur even before the T wave begins to be inscribed and fail to evoke a ventricular response because the ventricle is completely refractory.

tions (24) and changes in phase 2 of the action potential (25). The tracing in Figure 2, reproduced with modifications from part of Figure 3 in the study by Weintraub et al. (1), lends itself admirably to a better understanding of the electrophysiologic mechanisms underlying this peculiar electrocardiographic (ECG) manifestation. If the analysis is focused on beats 3 to 6 (showing the largest T wave change), it is apparent that in addition to the impressive T wave alternans, there is a less striking but definite alternation of both the QT and TQ intervals. In beats 3 and 5, these intervals measure, respectively, 700 ms and 0, whereas in beats 4 and 6, these intervals measure, respectively, 560 and 160 and 560 and 220 ms. Because QT and TQ are reciprocal intervals, a longer QT interval must naturally be followed by a shorter TQ interval and vice versa, provided the heart rate is relatively constant. Conversely, in beats 3 and 5, the T waves are *concordant* (26), suggesting that there is a gradient in the duration of action potentials causing repolarization to proceed essentially from epicardium to endocardium.

The duration of the action potentials should be longest in the subendocardial layers (note that the QRS complex looks like a recording facing the lateral wall of the left ventricle). Because the QT interval is a good approximation of the action potential duration in regions where repolarization lasts longer (27,28), it can reasonably be estimated that the action potential duration was approximately 700 ms in the subendocardium of the left ventricular free wall and significantly shorter in the subepicardium. Just the opposite occurs in beats 4 and 6, in which the T waves are *discordant* (26); repolarization proceeds from endocardium to epicardium and *action potential duration must be longest in the subepicardium* (approximately 560 ms) and shorter in the subepicardium.

Figure 2. T wave alternans (reproduced with modification from Fig. 3, Ref. 1). The TQ and QT intervals are in ms. Numbers in EPI and ENDO indicate the approximate estimation of the action potential duration and its variation from beat to beat in the subepicardial and subendocardial layers of the left ventricular wall, respectively. For further discussion, see text.



These data have been used to construct the scheme in Figure 2B, assuming that action potential duration and diastolic interval are equivalent to QT and TQ intervals considered separately for subendocardium and subepicardium. Because there is no information about QT and TQ intervals in the subepicardium in beats 3 and 5, it has also been assumed that these intervals remain constant in all beats 3 to 6. The reasons for this assumption follow. To discuss the scheme in Figure 2B, it is convenient to consider separately the alternation of the QT and TQ intervals and the T wave alternation.

Mechanism of QT and TQ alternation. Two related factors play a major role in the mechanism of QT and TQ alternation. 1) Whenever the QT interval is disproportionately long and the cardiac rate *relatively* fast, cardiac impulses tend to occur close to the preceding T wave and to behave physiologically as though they were "premature." 2) In a classic study on isolated (perfused) ventricular muscle, Gettes et al. (29) demonstrated that premature impulses with a "proximity" (diastolic interval) >150 ms failed to result in any shortening of the action potential duration, whereas a significant abbreviation occurred when proximity was <150 ms, particularly between 60 and −20 ms. These results serve to explain why beat 4 in Figure 2B with a proximity (preceding TQ interval) of 0 behaves as a very premature beat and results in a 140-ms shortening of the QT interval (from 700 ms in beat 3 to 560 ms in beat 4). This shortening in turn results in a prolongation of the following TQ interval (from 0 to 160 ms); beat 5 behaves like a "nonpremature" impulse and its QT interval returns to the initial value of 700 ms. This again shortens the TQ interval from 160 to 0 ms, and the process repeats itself in the succeeding beats as long as the heart rate remains constant. Thus, alternation of both the QT and TQ intervals appears to be a simple consequence of any abrupt increase in heart rate, initially causing a marked or sufficient shortening of the TQ interval to a value <150 ms. This sequence does not even require an abnormally prolonged QT interval. In fact, alternation of the action potential duration in isolated ventricular muscle (27,30) or in the duration of refractoriness in the intact canine heart (31) has been shown to result from an abrupt acceleration of the rate of stimulation, as theoretically predicted by Lepeschkin (32) for the T wave many years ago and even noted to occur in a theoretic model of the

action potential of Purkinje fibers (33). However, alternation of the QT and TQ intervals is greatly favored by a disproportionate prolongation of the QT interval, as has often been seen in reported cases of either congenital (1,9,21,23) or acquired (34–37) long QT syndrome.

Mechanisms of T wave alternans. If the shortening-lengthening of the action potential duration underlying the QT and TQ alternation occurred uniformly throughout the ventricle, there would be no reason for the morphology and, in particular, the polarity of the T wave to change. For T wave alternation to occur, these effects must be of dissimilar magnitude in different parts of the ventricle, particularly in subendocardial and subepicardial layers of the left ventricle, as hypothetically depicted in Figure 2B. Although there is no information about the possible action potential duration in beats 3 and 5, the preceding TQ intervals (200 and 160 ms, respectively) suggest that it could not have been much different from that in beats 4 and 6.

This hypothesis is supported by recent studies (38–40) demonstrating that the electrical properties of isolated subendocardial and subepicardial muscle may exhibit striking differences. The action potential shows a spike and dome configuration only in the subepicardium. Also, and more pertinent, there is a difference in the response of action potential duration to changes in the rate of stimulation; the curve expressing this relation is much steeper in the subepicardium (39,40). This results in a *crossover* of both curves so that the action potential duration is shorter in the subepicardium below a given cycle length and longer above the same cycle length. Also, the restitution of action potential duration (when tested by premature impulses) is much steeper in the subepicardium. These results lend credibility to the mechanism depicted in Figure 2B, particularly to the crossover of action potential durations from beat to beat, which is essential to cause the drastic reversion in polarity of the T wave. Accordingly, we propose that the QT, TQ and T wave alternations are mostly the expression of properties that are inherent to the normal subepicardial-subendocardial electrophysiology and brought out by an exaggerated prolongation of the action potential duration and the QT interval such as commonly occurs in the long QT syndromes. The differences between subepicardium and subendocardium are related to the existence of a transient outward current in the former but not in the latter (38). This current, held responsible for phase 1 of early repolarization, is one of the several potassium currents that modulate the process of repolarization (41,42). This transient outward current channel may well be one target for future research regarding the still unknown mechanisms of long QT syndromes.

Why and When 2:1 Pseudo AV Block or the T Wave Alternans Occurs

Role of heart rate versus QT duration. Like obvious T wave alternans, pseudo 2:1 AV block can be considered a form of alternating electrical activity of the heart and both are clearly rate dependent. Why and when does one or the other occur? An impressively simple answer to this question is provided in Figure 1 of a recent study (43). In a theoretic Beeler-Reuter model of a *single* ventricular cell, an abrupt change in the basic cycle length from 1,000 to 300 ms resulted in alternans of the action potential duration (with clear alternation of the diastolic intervals), whereas a change in cycle length from 1,000 to 250 ms resulted in 2:1 responses. It is therefore not surprising that one or the other may occur in long QT syndromes, depending on the heart rate versus the QT duration. A beautiful example in which both were seen at different moments in the same patient was reported by Sharma et al. (9).

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